REVIEW

Addressing the Symptoms or Fixing the Problem? Developing Countermeasures against Normal Tissue Radiation Injury

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INTRODUCTION

The successful development of countermeasures for radiation-induced damage to normal tissue could potentially benefit a broad range of populations and conditions. At one end of the spectrum are patients in a therapeutic setting where prevention or mitigation of acute and delayed normal tissue effects might improve survival; an improved therapeutic ratio would offer clinicians the opportunity to raise radiation dose limitations, thereby increasing tumor cure rates. An additional benefit would be an improvement in the quality of life of survivor populations, a growing concern at the National Cancer Institute (1, 2). At the other end of the spectrum are personnel affected by a mass casualty situation such as a deliberate or accidental nuclear or radiological event (3). Unlike approaches that might be of use in the highly defined clinical setting, countermeasures that would be utilized in an emergency event require broad activity since they will be targeted to radiation injuries resulting from, in all likelihood, relatively unknown dose exposures, involving heterogeneous volumes that may have affected multiple tissues and organs. Furthermore, agents in this category must be easily deliverable with minimal (or preferably no) toxicities (4, 5). Although overall, this latter category of countermeasures may prove to have little immediate apparent commercial value other than placement in the strategic national stockpile, however the potential does exist for crossover usage in the clinic, as well as for the equally broad need of reducing the risk of delayed or late effects such as carcinogenesis, cataracts, cardiovascular disease, etc. (6) The potential risk for late effects is not limited to acute high doses, but also prolonged low-dose exposures associated with occupational or environmental exposures (7), as well as the chronic exposures to high-linear energy transfer (LET) cosmic radiation encountered by astronauts during long-term missions (8). It remains unclear whether this spectrum of conditions will respond to similar mitigation strategies.

Given such a broad potential market, it is not surprising that many researchers have chosen normal tissue radiation biology as their field of interest. The importance of this field to advancing cancer therapy, particularly for radiation oncologists, is underscored by the number of past and current world-renowned experts in the field of radiation research who dedicated their careers to this area, including Julianna Denekamp, Rodney Withers, Elizabeth Travis and Richard Hill, to name just a few. However, to develop valid radiation countermeasures, particularly for emergency use in the U.S., there is a Food and Drug Administration (FDA) licensure requirement for a clear understanding of the biology that underlies the target condition (9, 10), i.e., knowledge of the mechanisms that lead to the development of radiation-induced normal tissue effects. Unfortunately, the random nature of ionizing radiation injury at both the cellular and tissue levels and the complexity of the resultant pathological and physiological changes have combined to confound investigators, despite decades of research, so that the development of viable radiation countermeasures for either the clinic or accidental exposure has remained relatively elusive. The resurgence of interest in this field, prompted by the events of 9/11 and, more recently in Fukushima, has opened new insights and may offer some degree of hope (11). This review offers a reflection on how